

isolated a purified salmon sperm DNA for 12 hours at approximately 40°C followed by washing twice for 30 minutes in 2 x SSC, 0.5% SDS at a temperature of at least 45°C and wherein said polynucleotide encodes an amino acid sequence having activity as a KCNQ4 potassium channel subunit.

REMARKS

Claim 1 has been amended to additionally require that the amino acid sequence encoded by the polynucleotide has activity as a KCNQ4 potassium channel subunit. Support for this amendment can be found throughout the Specification, for example, on page 13, lines 2-3 and page 18, lines 15-21. No new matter has been added.

Rejections Under 35 U.S.C. § 112, First paragraph

Enablement

The Examiner has maintained his rejections of claims 2, 10, 11, 21 and 22, and now rejects claims 1, 3-6, 10-11, 18-29 and 59-61 for lack of enablement. The Examiner contends that while the Specification is enabling for an isolated polynucleotide having the sequence of SEQ ID No: 1, it does not provide enablement for an isolated polynucleotide that is at least 90% homologous to the nucleotide sequence set forth in SEQ ID No: 1. As stated in Paper No. 12, the Examiner contends that because there are reports in the

part of a single amino acid change having a dramatic effect on a protein's function, one of ordinary skill in the art would need to perform undue experimentation in order to obtain the instant invention. The Examiner also contends that there is insufficient enablement for identifying an isolated polynucleotide capable of hybridizing under the conditions set forth in claim 1 to the polynucleotide sequence of SEQ ID NO: 1. The Examiner concludes that a substantial number of hybridizing or complementary polynucleotides would not share either structural or functional properties with a polynucleotide encoded by SEQ ID NO: 1. The Examiner also states "the Specification fails to provide an enabling disclosure of how one would use such polynucleotides."

The Examiner supports his contentions by referring to a 1990 Science reference (Bowie et al.). Bowie teaches that the problem of predicting protein structure from sequence data and in turn using the predictive structural determinations to predict functional aspects of the protein is extremely complex. Bowie also states that certain positions in the sequence of the protein are critical to the three dimensional structure/function relationships. From this, the Examiner concludes that it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention. Applicants respectfully traverse.

Applicants first point out that the active clone of KCNQ4 (SEQ ID No: 1) has been identified. A non-functional mutation "G938A,

has also been identified. Moreover, under no priors are disclosed in pages 1-11 of the Specification which may be used to amplify additional sequences. Considerable information is provided concerning the structure of KDNQ4, for instance conserved regions page 14, lines 1-21. Additionally, the method of screening candidates for KDNQ4 activity is disclosed in Example 4 (pages 26-30). The active clone (SEQ ID No: 1, and the non-functional mutation (G953A) can thus serve as positive and negative controls in, for example, the assay disclosed in Example 4.

In Paper No. 12, the Examiner correctly states "the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." Generation and/or identification of sequence variants were routine experimental and laboratory practice by February 1, 1999, when the instant application was filed. Within the Specification, Applicants have provided all of the tools necessary in order to carry out either the generation of variant sequences or the identification of them. For example, one skilled in the art would recognize that the active clone could be used as a basis for mutagenesis. The sequence variants that would be obtained could easily be screened using the functional assay described in Example 4. The fact that the Applicants have not detailed each and every method available to produce variants or to identify appropriate variants is not problematic. A patent need not teach and

primarily what is well known in the art. In re Buchner, 929 F.2d 1171, 1181, 18 USPQ2d 1331, 1333 Fed. Cir. 1991. Time and difficulty of experiments are not determinative if they are merely routine. MPEP 2104.06. Thus, in view of the disclosure in the Specification of all of the tools necessary for making and using the instant invention, the routine nature of the experimental procedures involved and the fact that there was a high level of skill in the art at the time the Application was filed, the disclosure of the instant Specification is enabling for an isolated polynucleotide that is at least 90% homologous to the nucleotide sequence set forth in SEQ ID No: 1. Furthermore, the Specification clearly states that these sequences can be used for drug identification and in screens for identifying the source of hearing loss in humans as well as for the production of mammalian disease models, such as recombinant mice (see page 3, line 16 to page 4, line 6).

The Bowie et al. reference that the Examiner cites, is not particularly relevant to the instant application. First, the reference was published in March of 1990, approximately nine years before the filing of the instant application. During those nine years, the field of protein structure and function prediction has advanced enormously, making much of what had required significant effort become routine. Second, the Bowie reference was primarily directed to developing making protein structure and function

predictions from the large amounts of sequence data that was being generated from the advent of the Human Genome Sequencing Project. While it remains true that certain positions in some proteins are critical to the three dimensional structure/function relationship, with the development of more sophisticated cloning and screening techniques, the skilled artisan is no longer required to conduct analysis on a sequence-by-sequence basis. Indeed, in February of 1999, when this Application was filed, it was possible to produce and screen hundreds and thousands of sequences using common laboratory techniques and a functional assay, such as that described in Example 4, within a very short period of time. Thus, again, because of the substantial and significant advances in the art, a skilled artisan would not be required to expend undue experimentation in order to obtain the instant invention.

In view of the above discussion, Applicants respectfully request reconsideration and removal of the rejection.

Written Description

The Examiner has maintained his rejections to claims 2, 10, 11, 21 and 22, and now rejects claims 1, 3-6, 10-11, 18-29 and 59-61 as lacking written description. The Examiner justifies his rejection stating that these are genus claims and that the Specification, while disclosing that the polynucleotide of the invention may have an amino acid change at one or more positions,

does not indicate what distinguishing attributes are shared by the members of the genus. The Examiner goes on to say that sequences identified by hybridization would not predictably have the same structural and functional characteristics because there is no way to determine what variations would be tolerated. He concludes that since the Specification fails to describe a sufficient number of each genus and because one of skill in the art could not be expected to predict biological activity of the sequence variants encompassed by the claims, the written description requirement has not been met. Applicants respectfully traverse.

Applicants first wish to point out that the Examiner's statement that sequences identified by hybridization would not predictably have the same structural and functional characteristic as the disclosed species is not correct. Hybridization is a function of both base pair content and base pair sequence. Thus, at the 90% homology level, two sequences would by definition share 90% structural homology with each other. In addition, the Synopsis Of Application Of Written Description Guidelines prepared for Examiners indicates in Example 9 that hybridization language is perfectly acceptable under circumstances that are similar to the present situation (please see enclosed).

Applicants also wish to point out that because the Specification describes a screening method that is based on the function of the biological activity of the sequences, the skilled

artisan has no need to "predict the biological activity" of the sequences obtained. The written description requirement for a genus claim can be satisfied if the species which are adequately described are representative of the entire genus. MPEP 2163.05. In the present case, Applicants have defined the species in terms of both structure i.e. 90% identical to SEQ ID NO: 1, and function. In addition, Applicants have provided alignment data indicating conserved, semi-conserved and lesser conserved regions within the KCNQ4 sequence. Thus, Applicants respectfully submit that they have met the written description requirement and request reconsideration and removal of the rejection.

Rejections Under 35 U.S.C. § 102

The Examiner has maintained his rejection of claims 1, 3-8, 10-11, 18-19 and 21-30, and now rejects claims 59 and 61 as being anticipated by Singh et al. (1998). The Examiner contends that the nucleotide sequence of a potassium channel, KCNQ2, would hybridize under high stringency conditions to the nucleotide sequence of SEQ ID NO: 1 of the instant application. The Examiner contends that since the polynucleotide would hybridize under the conditions set forth in the claims and the claims do not contain any functional limitations, the claims are anticipated. Applicants respectfully traverse.

Applicants first point out the claims now require that the polynucleotide of the instant invention encodes an amino acid sequence having the functional activity of a KCNQ4 potassium channel sub-unit. Applicants also submit that the Singh polynucleotide would be unable to hybridize to SEQ ID No: 1 of the instant invention. Applicants enclose the data available for KCNQ2 from the National Center for Biotechnology Information (NCBI). Applicants also enclose the results of an NCBI Blast 2 Sequences Program provided by NCBI with respect to SEQ ID No: 1 and the KCNQ2 polynucleotide. Here, the coding sequence of the two sequences (SEQ ID No: 1 and KCNQ2) have been aligned. As can be seen in the report, there is no significant homology determined over the entire sequence. The program was able to detect significant homology for only four partial (internal) sequences. These may be represented as follows:

Fraction 1: determined over 814 basis, 76% homology

Fraction 2: determined over 147 basis, 84% homology

Fraction 3: determined over 64 basis, 82% homology

Fraction 4: determined over 48 basis, 85% homology

Thus, of a total sequence of 2088 nucleotides of SEQ ID NO: 1, only 1073 basis (814+147+64+48) could be blasted, which corresponds to only 51.4% of the coding sequence. Overall this leaves a homology of less than 50% between the nucleotide sequence encoding the KCNQ4

channel of the instant invention and that of the KCNQ2 channel of Singh et al.

While the exact homology of sequences that are capable of hybridizing under high stringency conditions, depends on the particular sequences in question and can only be determined experimentally, some general guidelines are available. See, for example, current *Protocols In Molecular Biology*, Ausubel et al., Eds., John Wiley & Sons Inc., 1998, Vol. 1, comments to section 6.3.5: "High-stringency wash is determined empirically. The relative homology between the probe and target sequence is a determining parameter. If the homology is 100%, a high temperature (65° to 75°C) can be used. As the homology drops, lower washing temperatures must be used." Thus, under the conditions set forth in claim 1, it is fair to expect a homology in the order of 80-100% to be capable of surviving the hybridization conditions. Thus, KCNQ4 disclosed by Singh et al. will not hybridize with SEQ ID NO: 1 of the instant invention.

In view of the above, Applicants respectfully request reconsideration and removal of the rejection.

Rejections Under 35 U.S.C § 103

The Examiner maintains his rejection of claims 1, 3-8, 10-11, 18-19 and 21-30, and now rejects claims 59 and 61 as being unpatentable over Singh et al in view of WO9401548 (Sibson et al.).

The Examiner's contentions concerning the Singh et al. reference are set forth above. Singh et al. does not teach methods of producing a protein. The Examiner contends that it would have been obvious to one of ordinary skill in the art to modify the invention of Sioson et al. by substituting a cDNA in the polycloning region of the vector with the polynucleotide of Singh et al. for the purpose of transfecting host cells. The Examiner maintains that one of ordinary skill in the art would have been motivated to make the substitution in order to express the protein encoded by the introduced DNA (i.e. that of Singh et al.) in a host cell to perform ligand binding and functional assays. The Examiner notes that since these techniques are widely used in the art and are highly successful, there would have been a reasonable expectation of success. Applicants respectfully traverse.

As discussed above, the Singh et al. polynucleotide which encodes the KCNQ4 channel protein does not hybridize to SEQ ID NO: 1 under the conditions set forth in claim 1 or claim 2. Because of this, Singh et al. alone does not support a case for obviousness. Neither does the combination of Singh et al. and Sioson. Here, despite potential for expressing a protein encoded by the introduced DNA in a host cell, because the Singh et al. sequence does not possess the required structural and functional attributes, the instant invention could not be obtained. Thus, whatever ligand binding and functional assays could be performed

would not produce the results expected by the instant invention because the polynucleotide encoding PCN24 fails to meet the structural homology requirement and the functional requirement stated. Consequently, Applicants respectfully request reconsideration and removal of the rejection.

In view of the above remarks, all of the claims remaining in the case are submitted as defining novel, non-obvious, patentable subject matter.

If the Examiner has any questions concerning this application, the Examiner is requested to contact the undersigned at 714-708-8555 in Costa Mesa, CA. to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), the Applicants respectfully petitions for a one (1) month extension of time for filing a response in connection with the present application and the required fee of \$110.00 is attached hereto.

Attached hereto is a marked-up version of the changes made to the application by this Amendment.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of
time fees.

Respectfully submitted,

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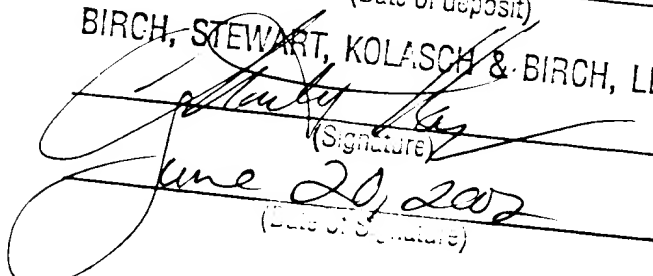
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Attachment: Version with Markings to Show Changes Made

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

CLAIMS:

The claims have been amended as follows:

1. Thrice Amended An isolated polynucleotide having a nucleic acid sequence which is capable of hybridizing under high stringency conditions with the polynucleotide sequence of SEQ ID No: 1, or its complementary strand, wherein said hybridizing occurs in a solution of 5 x SSC, 5 x Denhardt's solution, 0.5% SDS and 100 ug/ml of denatured sonicated salmon sperm DNA for 12 hours at approximately 45°C followed by washing twice for 30 minutes in 2 x SSC, 0.5% SDS at a temperature of at least 65°C and wherein said polynucleotide encodes an amino acid sequence having activity as a KCNQ4 potassium channel subunit.

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